

REMARKS

A. Status of Claims and Amendment

This Amendment, filed in reply to the Office Action dated July 7, 2009, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 6, 9, 11, 17-20, 22, 24, 26, 28, 30-34, 36, 38, 40 and 42 are all the claims pending in this application, and are rejected. Claims 6, 17-20, 22, 24, 26, 28, 30, 32 and 38 are canceled herewith without prejudice or disclaimer. Claim 9 is amended herewith. Support for this amendment can be found throughout the specification as filed, and at, for example page 16, lines 22-35.

No new matter is added by way of this amendment. Entry and consideration of this amendment are respectfully requested.

B. Withdrawn Rejection

Applicants thank the Examiner for withdrawing the rejection of claims 6, 9-11, and 17-42 under 35 U.S.C. § 103(a) as being unpatentable over Shih *et al.* (U.S. Patent Publication No. 2002/0172989)(“Shih *et al.*”) in view of Olsen *et al.* (WO 98/30682A1)(“Olsen *et al.*”), and further in view of Genov *et al.* (Biochem J, 1982, Vol. 207, p.193-200)(“Genov *et al.*”).

C. Rejection under 35 U.S.C. § 103

Claims 6, 9, 11, 17-20, 22, 24, 26, 28, 30-34, 36, 38, 40, and 42 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Shih *et al.* in view of Olsen *et al.* and further in view of Genov *et al.* for essentially the same reasons already of record. Further, in response to Applicants’ arguments made on May 29, 2009, the Office Action asserts that Applicants’ evidence of unexpected properties of enzyme digestion without preheating is not sufficient to

rebut a *prima facie* case of obviousness because the prior art teaches the use of proteolytic enzymes (including a subtilisin) in the method for digesting infectious prion proteins and treatment temperature of the tissue before its exposure would have depended on the proteolytic activity of the enzyme. Therefore, the Office Action concludes that Applicants' evidence does not show unexpected results or establish nonobviousness "because it is not sufficient to establish that a person of ordinary skill in the art at the time of the invention was made **would have not been motivated** to use the enzyme taught by the prior art in the method of Shih to provide a method for digesting infectious prion proteins and a method for detoxifying a pathologic prion protein with a reasonable expectation of success." Emphasis added, see pages 7-8 of the Office Action dated July 7, 2009.

Applicants respectfully traverse and submit that the Office Action appears to have discounted Applicants' unexpected results and improperly applied the law of obviousness.

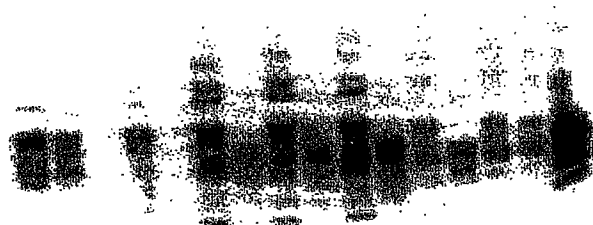
Initially, it is jurisprudentially inappropriate to disregard any relevant evidence, including secondary considerations in an obviousness determination. Evidence of "secondary considerations" must, when present, be considered in determining obviousness. See *Pro-Mold v. Great Lakes Plastics*, 75 F.3d 1568 (Fed. Cir. 1996). Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record. *Id.* (Secondary considerations "are often most probative and determinative of the ultimate conclusion of obviousness or non-obviousness."). In fact, many cases have held that, although called "secondary considerations", such considerations are not secondary in importance, and that all the considerations must be weighed before deciding obviousness. See *Truswal Systems Corp. v. Hydro-Air Engineering, Inc.*, 813 F.2d 1207 (Fed. Cir. 1987) ("Although secondary in time, secondary considerations are not secondary in importance and may be highly relevant as indicia

of non-obviousness”). *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 958 (Fed. Cir. 1997)(“The district court’s statement that ‘secondary considerations are just that -- secondary’ suggests a misperception of the role of these considerations in determination of the ultimate question.”). Thus, even if an alleged motivation to combine has been cited, the Office is required to review secondary considerations, such as unexpected results in an obviousness determination.

The claimed method, as amended, recites a method for digesting a protein, “wherein the contacting step is carried out without preheating the subject” and “wherein said enzyme is produced by *Bacillus licheniformis* MSK-103.” The claimed method is nonobvious over the prior art for at least the following reasons.

The expectation created by Shih is that protein digestion with an enzyme is effective when the sample is subject to preheating. Specifically, the method of Shih discloses a pretreatment step to “cook” the tissue at a temperature from about 100°C to about 150°C in order to completely destroy the prion proteins in tissue (see paragraph [0017] of Shih). Figure 1 of Shih illustrates a gel electrophoresis/Western blot showing the digestive effect of keratinase in infectious prior protein when the samples were precooked and when the samples were not precooked. For convenience, Figure 1 is reproduced below:

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17

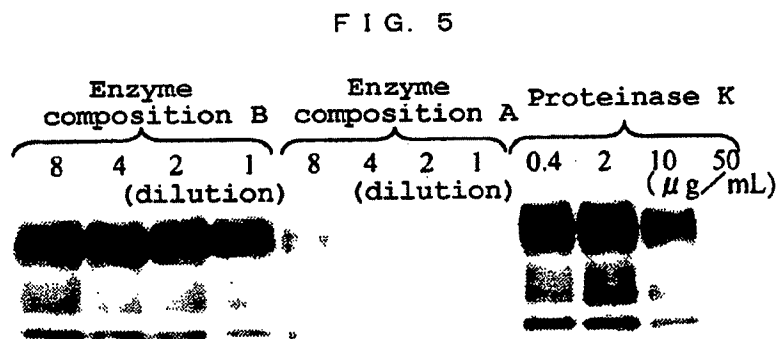


Lanes 3-6 show the digestive effect of keratinase when the samples were precooked at 115°C for 40 minutes. Lanes 7-10 show the digestive effect of keratinase when the samples were not precooked. As clearly illustrated above, without precooking, keratinase was less effective at digesting the protein than when the sample was cooked. In particular, Lanes 3 and 5 show that almost all the infectious prion material was destroyed, while Lanes 7-10 show that approximately half of the infectious protein was not degraded. Furtherstill, a publication that was coauthored by Shih² discloses that keratinase enzyme was effective when it was preheated at temperature above 115°C and discloses little effectiveness when it was heated at 70-90°C. Thus, as stated above, the expectation created by Shih is that protein digestion with an enzyme is effective when the sample is subject to preheating.

In contrast, Applicants' claimed method expressly recites a method wherein the contacting step is carried out without a preheating step. The instant specification shows the efficacy of degrading infectious material with an enzyme produced by *B. licheniformis* MSK-103, without subjecting the solution to preheating. For example, Examples 7 and 8 show that the enzyme as claimed exhibits an extremely high activity of digesting a pathogenic prion protein in comparison with the enzyme disclosed in Shih when the samples are not subject to preheating. Specifically, Example 7 states that digestion with Enzymes A (produced by *B. licheniformis* MSK-103) and Enzyme B (produced by *B. licheniformis* PWD-1) was carried out by incubating

² Langeveld *et al.*, Enzyme Degradation of Prion Protein in Brain Stem from Infected Cattle and Sheep, the Journal of Infectious Diseases, 2003:188, pages 1782-1789. In accordance with M.P.E.P. § 609.05(c), the documents cited herein in support of Applicants' remarks are being submitted as evidence directed to an issue raised in the Official Action, and no fee pursuant to 37 C.F.R. 1.97 or 1.98, or citation on a FORM PTO/SB/08A & B is believed to be necessary.

the mixture at 37°C for 1 hour--i.e., the mixtures were not subject to pretreatment. The results of Example 7 are illustrated in Figure 5 and shown below for convenience:



As clearly illustrated above, the enzyme of the present invention (Enzyme A, produced by *B. licheniformis* MSK-103) almost completely digested the pathogenic prion protein compared to enzyme B (the same enzyme disclosed by Shih) when the solution was not subjected to preheating. See also page 38, lines 4-19. Example 8 and Figure 6 similarly show the claimed enzyme provides unexpectedly superior enzyme digestion of prion proteins in comparison to the keratinase derived from *Bacillus licheniformis* PWD-1 when the solution is not subject to preheating. See page 38, line 20 to page 39, line 30. Thus, Applicants surprisingly found the claimed enzyme digests the infectious protein without thermal pretreatment. See page 4, lines 17-21.

In this regard, Applicants have shown by comparison to the closest prior art, Shih³, that the presently claimed method results in unexpectedly superior enzyme digestion without preheating a subject tissue; this could not have been predicted based upon the teachings of Shih and Olsen/Genov, either alone or in combination⁴. Such unexpected properties are evidence of the non-obviousness of the claimed invention, and **must be considered** by the Examiner, regardless of any alleged motivation to combine references. See *Pro-Mold v. Great Lakes Plastics*, 75 F.3d 1568 (Fed. Cir. 1996)(Secondary considerations “are often most probative and determinative of the ultimate conclusion of obviousness or non-obviousness.”).

Further, in one instance at page 3, paragraphs 0038-0039, Shih suggests that an initial heating is not required if the enzyme can completely degrade the infectious prions without preheating. Shih, however, fails to identify which, if any, enzymes are effective at degrading infectious prions without preheating. Thus, the discover of an enzyme that can digest a protein highly resistant to denaturation and degradation without preheating is unexpected.

Accordingly, Applicants respectfully request withdrawal of the rejection.

³ Although evidence of unexpected results must compare the claimed invention with the closest prior art, Applicant are not required to compare the claimed invention with subject matter that does not exist in the prior art. *In re Geiger*, 815 F.2d 686, 689 (Fed. Cir. 1987) (Evidence rebutted *prima facie* case by comparing claimed invention with the most relevant prior art. The Court held the Office failed to establish a *prima facie* case of obviousness.); *In re Chapman*, 357 F.2d 418, 148 USPQ 711 (CCPA 1966) (Requiring applicant to compare claimed invention with polymer suggested by the combination of references relied upon in the rejection of the claimed invention under 35 U.S.C. 103 “would be requiring comparison of the results of the invention with the results of the invention.” *Id.* at 422).

⁴ The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007) suggested that the standard for determining whether a patent claiming a combination of prior art elements would have been obvious should focus on “whether the improvement is more than the predictable use of prior art elements according to their established function.” *KSR* at 1740. Accordingly, a *prima facie* case of obviousness may be rebutted by a showing of unpredicted or unexpected results.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,


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